REMARKS

The applicants thank the Examiner and Practice Specialist Brian Stanton for the personal interview with the undersigned and with applicant William F. Dove on August 4, 2000. The applicants and the undersigned appreciated the prior opportunity to speak with the Examiner and the Practice Specialist. Should the need for another such discussion arise, the applicants and the undersigned stand ready to participate.

One outcome of the personal interview was a decision by the Examiner to issue a new requirement for restriction and that is the action taken by the Examiner on September 12, 2000. It is the understanding of the undersigned that the prior requirement for restriction and the prior Office Action on the merits are rendered moot by the Examiner's decision to issue a new requirement for restriction that includes all of the pending claims. Applicants note, however, that the claim amendments submitted in a response filed April 7, 2000 were entered and are reflected in the claims now pending.

Requirement for Restriction

In the requirement for restriction, the Examiner restricted the claims into seven groups. The applicants provisionally elect Group I (Claims 1-9), with traverse. The bases for the traversals are detailed below in a response to each of the Examiner's reasons.

Inventions I-III and IV-VII are said to be related as process of making and product made. The Examiner asserts that the inventions are distinct because the product as claimed in Groups IV-VII can be made by another and materially different process than that of Groups I-III. The Examiner named a general process for producing genetically altered mice or other non-human animals, but did not demonstrate that it is feasible today to make the claimed product by a transgenic technique. Under MPEP 806.05(f), the Examiner must demonstrate that the product as claimed can be made by another materially different process. The applicants respectfully invite the Examiner to document the present viability of such a technique as it relates to the claimed animals. Specifically, the applicants ask how today's skilled artisan would *a priori* choose a polynucleotide sequence that modifies an index phenotype for use as a suitable transgene? While transgenic techniques may yet be developed for producing mice that fall within the scope of hte product claims, applicants traverse this requirement for restriction because the Examiner has not identified an alternate method of making the animals of the invention that is practical today.

The Examiner next asserted that Inventions I-III are distinct from one another as requiring "different technical considerations and starting materials, and having different method steps." The applicants cannot determine the basis under 35 U.S.C. §121 or 37 C.F.R. §1.141 for this restriction requirement. Under the cited sections, the Examiner may require restriction if two or more "independent and distinct" inventions are claimed. MPEP §802.01 et seq. clarify the meanings of the terms independent and distinct and upon review, the

suitable bases for requiring restriction do not appear to include different technical considerations, starting materials, and method steps. To be "independent" there must be no disclosed relationship between the subjects disclosed. The inventions must be "unconnected in design, operation, or effect." MPEP §802.01.

Surely the claims of Groups I, II, and III do not meet that standard of independence, as would those in the examples of MPEP §802.04 (e.g., a process of painting a house and a process for boring a well). Instead, until the invention by the applicants, no process was known for identifying segregating mutations at a genetic locus that modify an index phenotype in a non-human animal such as a mouse. That invention is reflected in both Claim 1 (Group I) and Claim 10 (Group II) which are identical, except for the addition of steps in Claim 10 for identifying a human sequence from a sequence previously identified in a non-human animal. These additional steps alone are not novel, in and of themselves, for the applicants acknowledge at page 11 of the specification that once a modified phenotype is identified, it can be cloned from the animal and the corresponding sequences in humans can also be obtained using technology available to the skilled artisan. However, applicants maintain that the prior steps shared between the groups support patentability of the claims.

With regard to Group III, the applicants first point out the complete identity in the Office Action between both the description and classification of the Group III claims with those of Group I. This would suggest that the claims should be examined together. While certain aspects of the claims are indeed different from Groups I and II and reflect method refinements, all the method claims identify a segregating mutation at a genetic locus that modifies an index phenotype. Notably, all employ animals that carry a dominant allele at a locus known to confer the index phenotype along with random point mutations that are screened for their ability to modify the index phenotype. Thus, the points of similarity between the methods of Groups I-III far outweigh any technical differences among them. It is without doubt an undue burden on the applicants to force the applicants to examine each set of method claims in a separate application, especially where all sets of method claims share common novel and inventive features.

The same is true with regard to Inventions IV-VII. The reliance upon different technical considerations and starting materials and different method steps is not believed to be sufficient to warrant restriction. Rather, the inventions must be independent and distinct as those terms are defined in the statute and rules of practice. In describing the asserted differences among Groups IV-VII, the Examiner has overlooked the features shared by the animals in each group. Specifically, all animals include a dominate heterozygous allele that confers an index phenotype and all include a segregating modifier of the index phenotype attributable to a point mutation. The fact that different method steps are employed is a result of ongoing improvements in the methods by the applicants to improve the quality of the resulting animal. At their core, however, the similarity of the animals produced in Group IV

and in the product-by-process claims, again far outweigh the differences among them. It is beyond the scope of this response to detail the evolution of the method from the methods and products of the parent application to those so-called "compact screen" and "isogenic background" methods and products of this CIP application. These points were, however, discussed during the aforementioned personal interview.

While applicants provisionally elect Group I with traverse, applicants respectfully request that Group I be redrawn to include Claims 1-16 for the reasons noted above. Moreover, for the reasons noted at the outset, applicants further believe that the Examiner has not met the burden of demonstrating that the method claims are independent and distinct from the product claims as required by 35 U.S.C. §121 and, accordingly, that the requirement for restriction between methods and products should be withdrawn.

Claim amendments

During the personal interview, the Examiner asked the applicants submit a narrower claim for search and examination purposes. Applicants have attempted to comply with the Examiner's suggestion by presenting new Claims 26-29 within the scope of provisionally elected Group I. Applicants present these claims with the understanding that no broader subject matter is being given up or cancelled by the applicants. It is in that spirit that the applicants submit method Claim 26 that corresponds to a particular case of the steps recited in Claim 1. New Claim 26 depends from Claim 6, rather than from Claim 1, as the founder inbred strain (C57BL/6) and the index inbred strain (C57BL/6-*Min* Congenic) share an isogenic genetic background. This is advantageous and preferred, but is not a requirement of the invention in its broadest embodiment. Support for Claim 26 is found in the first full paragraph on page 15. Claim 27, which depends from Claim 26, recites a statistical method for evaluating modified tumor multiplicity in the N2 backcross progeny. Support for the statistical methods of Claim 27 is found on page 15, line 25 through page 16, line 28. New Claim 28 further incorporates a step of mapping the segregating mutation, while new Claim 29 recites the particulars of making a suitable SNP mapping partner strain. Support for Claims 28 and 29 is found in the paragraph that bridges pages 14 and 15.

Certain amendments to Claims 6 and 7 are also presented. These amendments correct technical inconsistencies in pending Claims 6 and 7.

A petition for three months extension of time accompanies this response so that the response will be deemed to have been timely filed. Should any additional extension of time be due in this or any subsequent response, please consider this a request for the appropriate extension of time and a request to charge any fee due in that regard to Deposit Account Number 17-0055.

Likewise, if any fees other than the additional claim fees are due in connection with this or any subsequent response, please consider this to be a request to charge the fees due to the same deposit account.

Reconsideration of the requirement for restriction, and entry of the preceding amendments and consideration of same are respectfully requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. A method for identifying a segregating mutation at a genetic locus that modifies an index phenotype in a non-human index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

outcrossing at least one male animal of a non-human founder inbred strain to at least one female animal of a non-human index inbred strain to obtain F_1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a congenic dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, wherein at least one of the F_1 progeny that carry the dominant allele also carry at least one random mutation;

backcrossing gametes from male F_1 progeny to at least one female of the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least one of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype; and

verifying that the outlying phenotype is caused by a segregating mutation.

2. A method as claimed in Claim 1 wherein any of the crosses employ preserved gametes.

3. A method as claimed in Claim 1 wherein the F_1 progeny and some of the N2 progeny exhibit an extreme outlying phenotype.

4. A method as claimed in Claim 3 wherein the segregating mutation is a heterozygous modifier of the index phenotype selected from a group consisting of an enhancing modifier and a suppressing modifier.

5. A method as claimed in Claim 1 wherein the dominant allele is a *Min* allele at an *Apc* locus in a mouse.

6. (Twice amended) A method as claimed in Claim 1 wherein the index inbred strain and the founder inbred strain share an isogenic genetic background [but can be distinguished by single nucleotide polymorphisms].

7. (Amended) A method as claimed in Claim 6 [wherein the isogenic index strain is produced by a method comprising the steps of] <u>further comprising the step of mapping the segregating mutation using a mapping partner strain produced by the steps of</u>:

treating an animal of an index strain with a mutagenic agent to induce point mutations in the treated animal;

crossing the treated animal to an animal of the index strain to produce F1 progeny; and

sib-mating F1 and subsequent generation progeny until detrimental and lethal mutations are eliminated.

8. A method as claimed in Claim 1 wherein the founder inbred mouse strain is produced by a method comprising the step of treating a wild-type inbred mouse with a mutagenic agent to induce point mutations.

9. A method as claimed in Claim 8 wherein the mutagenic agent is ethylnitrosourea.

10. A method for identifying a human genetic sequence that corresponds to a segregating mutation at a genetic locus in a non-human animal, the segregating mutation causing an outlying phenotype relative to an index phenotype in an index inbred mouse strain, the method comprising the steps of:

outcrossing a founder inbred non-human strain to an index inbred non-human strain to obtain F_1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, wherein some of the F_1 progeny that carry the dominant allele also carry at least one random mutation;

backcrossing the F_1 progeny to the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least some of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype;

verifying that the outlying phenotype is caused by a segregating mutation;

identifying genetic markers linked to the segregating mutation;

identifying a gene on a contig that encodes the segregating mutation; and

recovering human genetic sequences that correspond to the mutation-encoding gene.

11. A method for identifying a segregating mutation at a genetic locus that modifies an index phenotype in a non-human index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

crossing a non-human founder inbred strain with a non-human index inbred strain to obtain Gen1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a congenic dominant allele at a locus known to confer the index phenotype, the founder strain and the index strain sharing an isogenic genetic background, wherein some of the Gen1 progeny that carry the dominant allele also exhibit a modified index phenotype; and

verifying that Gen1 progeny that carry the dominant allele and exhibit a modified index phenotype carry a segregating mutation.

12. A method as claimed in Claim 11 wherein the genetic background has no modifying effect upon the index phenotype.

13. A method as claimed in Claim 11 wherein the genetic background has a modifying effect upon the index phenotype.

14. A method as claimed in Claim 13 wherein the genetic background has an enhancing effect upon the index phenotype, and wherein the Gen1 animals exhibit a suppressed phenotype relative to the index inbred strain.

15. A method as claimed in Claim 11 further comprising the steps of:

mapping the segregating mutation by crossing Gen1 animals that have the dominant allele and a modified index phenotype to a genetically distinguishable inbred strain; and

evaluating the progeny of the mapping cross.

16. A method as claimed in Claim 15 wherein the genetically distinguishable inbred strain shares an isogenic genetic background with the founder and index strains and further comprises single nucleotide polymorphisms relative to the founder inbred strain.

17. A genetically altered mouse comprising in its genome:

a congenic dominant heterozygous allele that confers an index phenotype on the mouse;

a segregating modifier of the index phenotype, the modifier being attributable to a single point mutation, and

a single nucleotide mapping polymorphism genetically linked to the single point mutation.

18. A mouse as claimed in Claim 17 wherein the dominant allele is a *Min* allele at an Apc locus.

19. A non-human animal comprising a segregating mutation that modifies an index phenotype, the animal being prepared according to a method comprising the steps of:

outcrossing at least one male animal of a founder inbred non-human strain to at least one female animal of an index inbred non-human strain to obtain F_1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a congenic dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, wherein at least one of the F_1 progeny that carry the dominant allele also carry at least one random mutation;

backcrossing gametes from male F_1 progeny to the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least one of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype;

verifying that the outlying phenotype is caused by a segregating mutation; and

selecting an animal that shows the outlying phenotype.

20. A non-human animal as claimed in Claim 19 wherein the non-human animal is a mouse.

21. A non-human animal comprising a segregating mutation that modifies an index phenotype, the animal being prepared according to a method comprising the steps of:

crossing a founder inbred strain with an index inbred strain to obtain Gen1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a congenic dominant allele at a locus known to confer the index phenotype, the founder strain and the index strain sharing an isogenic genetic background, wherein some of the Gen1 progeny that carry the dominant allele also exhibit a modified index phenotype;

verifying that Gen1 progeny that carry the dominant allele and exhibit a modified index phenotype carry a segregating mutation; and

selecting an animal that shows the outlying phenotype.

22. A non-human animal as claimed in Claim 21 wherein the non-human animal is a mouse.

23. A non-human animal comprising a segregating mutation that modifies an index phenotype, the animal being prepared according to a method comprising the steps of:

outcrossing a founder isogenic inbred strain with the index inbred strain to obtain Gen1F_1 progeny, the founder isogenic strain being heterozygous only for random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype, where at least some of the Gen1F_1 progeny carry both the dominant allele and at least one random mutation;

crossing a founder animal of the founder isogenic inbred strain to an animal of the founder strain that lacks the mutations to obtain inbred Gen2 offspring, where the founder animal has at least one outcrossed F_1 progeny that displays the outlying phenotype relative to the index phenotype;

outcrossing Gen2 offspring to the index strain to obtain Gen2F_1 backcross progeny, half of which, on average, carry the dominant allele that confers the index phenotype; and

verifying that a subset of the Gen2F_1 progeny shows the outlying phenotype; and

selecting an animal that shows the outlying phenotype.

24. A non-human animal as claimed in Claim 23 wherein the non-human animal is a mouse.

25. A method for identifying a segregating mutation at a genetic locus that modifies an index phenotype in a non-human index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

outcrossing a non-human founder isogenic inbred strain with the non-human index inbred strain to obtain Gen1F_1 progeny, the founder isogenic strain being heterozygous only for random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype, where at least some of the Gen1F_1 progeny carry both the dominant allele and at least one random mutation;

crossing a founder animal of the founder isogenic inbred strain to an animal of the founder strain that lacks the mutations to obtain inbred Gen2 offspring, where the founder animal has at least one outcrossed F_1 progeny that displays the outlying phenotype relative to the index phenotype;

outcrossing Gen2 offspring to the index strain to obtain Gen2F_1 backcross progeny, half of which, on average, carry the dominant allele that confers the index phenotype; and

verifying that a subset of the Gen2F_1 progeny shows the outlying phenotype.

26. (New) A method as claimed in Claim 6 wherein the method identifies a segregating mutation at a genetic locus that modifies tumor multiplicity in a C57BL/6 mouse congenic for the *Min* allele at the Apc locus, the method comprising the steps of:

outcrossing at least one male C57BL/6 mouse carrying random point mutations to a female C57BL/6 mouse congenic for the *Min* allele at the Apc locus to obtain F1 progeny, wherein at least one of the F1 progeny carries both the *Min* allele and a random point mutation; and

backcrossing gametes from male F1 progeny to at least one female C57BL/6 mouse congenic for the *Min* allele at the Apc locus to obtain N2 backcross progeny, wherein at least one of the N2 backcross progeny carries the *Min* allele and has a tumor multiplicity that is modified relative to tumor multiplicity in a C57BL/6 mouse congenic for the *Min* allele at the Apc locus, the modified tumor multiplicity being characteristic of the segregating mutation.

27. (New) A method as claimed in Claim 26 wherein the modified tumor multiplicity is evaluated according to a method comprising the steps of:

repeatedly applying for random permutations of mice among N2 backcross subkindreds a likelihood ratio test of the null hypothesis that no multiplicity modifier is segregating to obtain a p-value, wherein a p-value of less than 0.05 indicates a potential carrier of the segregating mutation;

when the p-value is less than 0.05, calculating, for each potential carrier that has offspring with information about tumor multiplicity, a LOD score for presence of the segregating mutation, wherein the LOD score is $\log_{10}$ of a ratio of the probability of offspring phenotype data if the potential carrier mouse carries a multiplicity modifier to the probability of offspring phenotype data if the potential carrier mouse does not carry a multiplicity modifier, and wherein the denominator probabilities are calculated from an estimated background distribution and the numerator probabilities are calculated from a mixture of the estimated background distribution and an estimated modified distribution, where the estimated distributions are obtained by the method of maximum likelihood; and

mapping LOD scores of the potential carriers, whereby animals having the highest LOD scores are likely carriers of the segregating mutation.

28. (New) A method as claimed in claim 26, further comprising the step of mapping the segregating mutation in the N2 backcross progeny using a mapping partner strain.

29. (New) A method as claimed in Claim 28 wherein the mapping partner strain is produced by the steps of:

treating a C57BL/6 mouse with a mutagen to introduce random point mutations;

crossing the treated mouse to a C57BL/6 mouse to produce F1 progeny; and

sib-mating F1 and subsequent generation progeny until detrimental and lethal mutations are eliminated.